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Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement

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Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement.

Background. Severe renal disease is a feature of anti-neutrophil cytoplasmic antibodies (ANCA)-associated small-vessel vasculitis. We evaluated patient and renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement at diagnosis during long-term follow-up.

Methods. Eighty-five patients were diagnosed between 1982 and 1996 and followed until 2001 allowing ≥5 years of follow-up. All patients were treated with prednisolone and cyclophosphamide. Univariate and multivariate analyses with patient and renal survival as dependent variables were performed.

Results. Of the 85 patients in this study, 17 (20%) died within one year after diagnosis. Of the 25 patients (29%) who were dialysis dependent at diagnosis, two remained dependent and two again became dialysis dependent after less than one year; nine died early without renal recovery. Risk factors for death occurring within one year in univariate analysis (RR, 95% CI) were age >65 years (6.5, 1.6–13.7) and dialysis dependency at diagnosis (3.6, 1.0–13). Twenty patients died beyond one year during the long-term follow-up. Male gender (4.7, 1.6–10) and developing dialysis dependency during follow-up (4.1, 1.4–12) were associated with poor outcome. Risk factor for renal failure within one year was dialysis dependency at diagnosis (29, 3.6–229). Of 64 patients dialysis independent one year after diagnosis, 12 patients became dialysis dependent during follow-up. A renal relapse was strongly associated with development of renal failure in long-term follow-up (17, 3.5–81).

Conclusions. Early death and failure to recover renal function in PR3-ANCA associated vasculitis is associated with age > 65 years and dialysis dependency at diagnosis. Long-term renal survival is determined by renal relapses during follow-up only. Slow, progressive renal failure without relapses is rarely observed in this group.

Small vessel vasculitides, such as Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA), are strongly associated with anti-neutrophil cytoplasmic antibodies (ANCA), which are either directed to myeloperoxidase (MPO) or proteinase 3 (PR3) [1–3]. These diseases can occur in any organ system but the respiratory tract and the kidneys are most frequently involved. Untreated, WG results in death within weeks to months. Since the introduction of cyclophosphamide and prednisolone as standard treatment, survival has improved dramatically from less than 20% at one year reported in 1958 [4] to at least a 60% five-year survival reported in the past ten years [5–8].

Although life-saving in many patients, treatment with cyclophosphamide and prednisolone is associated with severe morbidity and mortality, both at short-term and during long-term follow-up. Initiating aggressive immunosuppressive therapy in order to regain or conserve independent renal function in patients with ANCA-associated vasculitis with renal involvement is, therefore, dependent on the perceived prognosis of the patient. Previous studies have associated serum creatinine [9, 10] and kidney biopsy findings [9–12] at diagnosis, and the occurrence of renal relapses [13] with reduced renal survival in patients with pauci-immune necrotizing glomerulonephritis. Recently, we and others observed differences between groups associated with the different antigenic specificity of ANCA [reviewed in 14]. Previously, we studied the long-term outcome in patients with MPO-ANCA associated glomerulonephritis and found that proteinuria at diagnosis and during follow-up was the most important risk factor for the development of renal insufficiency [15]. Thus far, to our knowledge none of the studies have focused on long-term outcome of patients with PR3-ANCA associated vasculitis with renal involvement.

In the present study, we retrospectively analyzed patient and renal survival in patients with PR3-ANCA associated vasculitis with renal involvement that were diagnosed and followed in one single center. We investigated predictors of outcome at diagnosis and during follow-up, and examined the role of non-renal and renal relapses

Key words: antineutrophil cytoplasmic antibodies, Wegener's granulomatosis, glomerulonephritis, progressive renal disease, proteinase 3.

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on long-term survival and renal outcome in this patient population.

METHODS

Patients

We retrospectively identified all consecutive patients diagnosed with, treated and followed in our hospital for PR3-ANCA positive vasculitis with evidence of renal involvement (as determined by a biopsy showing necrotizing and/or crescentic glomerulonephritis [1] and/or by deterioration of renal function with glomerular erythrocyturia, erythrocyte casts and proteinuria) between January 1982 and January 1996. Patients were followed until January 2001. Surviving patients thus were followed for at least five years.

Treatment and follow-up

Patients were treated according to a standardized protocol [15]. The treatment consisted of oral cyclophosphamide (2 mg/kg) and prednisolone (1 mg/kg body weight) daily with a maximal oral prednisolone dose of 60 mg/day. Doses of cyclophosphamide were adjusted to maintain the leukocyte count above 4×10^9/L. Patients who presented with severe vasculitic manifestations such as alveolar hemorrhage, rapidly rising serum creatinine or gastrointestinal symptoms were initially treated with intravenous methylprednisolone 1000 mg daily for three days. Plasma exchange was added to the treatment regimen in case of disease progression or persistence of active disease. The latter was defined as persistence of major extrarenal symptoms or the presence of active necrotizing renal lesions in a repeat renal biopsy after two to four weeks of immunosuppressive therapy. After four to six weeks, the daily prednisolone dose was tapered by 10 mg every two weeks until the dose reached 30 mg, and thereafter by 5 mg every two to four weeks. Once remission was achieved the daily dose of oral cyclophosphamide was tapered by 25 mg every three months. Patients who experienced a renal relapse, or a life-threatening non-renal relapse, were treated according to the same protocol. Minor non-renal relapses were treated with 1 mg/kg body weight cyclophosphamide daily and a maximal oral prednisolone dose of 40 mg/day.

Patients were hospitalized for at least two to three weeks or longer when indicated. After discharge, patients visited our outpatient clinic at least every two weeks during the first three months after diagnosis, every four weeks until one year after diagnosis, and every six weeks thereafter. At each visit, patients were evaluated by the same physician for signs and symptoms of vasculitic disease and/or adverse effects of the treatment. In addition, blood pressure (BP) and weight were measured, serum creatinine, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, and ANCA titer [16] were determined, microscopic urinalysis was performed, and proteinuria and creatinine were determined in a 24-hour urine collection.

Definitions

Remission was defined as a stabilization or improvement of creatinine clearance in combination with the absence of glomerular erythrocyturia and erythrocyte cell casts and symptoms or signs attributable to active extrarenal vasculitis with CRP <10 mg/L. A non-renal relapse was defined as new or recurrent findings indicative of vasculitic disease without signs of renal involvement [17]. A renal relapse was defined either histopathologically by the presence of new necrotizing lesions in a renal biopsy or clinically by recurrence of microscopic glomerular erythrocyturia, erythrocyte cell casts, proteinuria and a decrease in creatinine clearance in a patient with a previously stable renal function [17]. Microscopic glomerular erythrocyturia was defined as 10 or more red blood cells, with more than 50% dysmorphic cells, per high power field (magnification $\times 400$) in the absence of a urinary tract infection or an indwelling catheter.

Statistical analyses

Data are presented as mean $\pm$ standard deviation unless stated otherwise. Continuous data between groups were compared using the Student *t* test and the Wilcoxon signed rank test when appropriate. Survival curves for patient and renal survival were calculated using Kaplan-Meier estimates for survival distribution. End point for renal survival analysis was the start of renal replacement therapy or death due to renal failure. Differences between groups in survival were analyzed with log-rank test, and multivariate analysis with Cox proportional hazards analysis with survival time as dependent variable was performed. Renal survival rates [survival without end-stage renal disease (ESRD)] are calculated and analyzed with subjects dying with independent renal function censored.

Analyzing patient and renal survival, a large difference between both patient and renal survival ≤ 1 year and >1 year after diagnosis became apparent. Survival differences between groups, therefore, were analyzed separately for the time periods ≤ 1 year and >1 year after diagnosis (long-term follow-up), to identify risk factors for these specific time periods. Independent variables tested in the analysis of patient and renal survival ≤ 1 year were age, gender, pulmonary involvement (with or without need for mechanical ventilation), CRP level, serum creatinine level, dialysis dependency, and Birmingham Vasculitis Activity Score (BVAS) [18] at diagnosis. Variables additionally tested for their association with long-term patient and renal survival (>1 year) were the occurrence of non-renal and renal relapses, cumula-

Table 1. Distribution of disease manifestations at diagnosis by organ system

Organ system	*N*	%
Renal	85	100
ENT[a]	72	85
Musculoskeletal	64	75
Pulmonary	47	55
Cutaneous	37	44
Neurologic	34	40
Ocular	29	34
Other[b]	19	22

[a] ENT, ear nose throat disease
[b] Including heart and gastrointestinal tract

tive doses of medication, mean arterial pressure (MAP), creatinine clearances and proteinuria at 12 months and use of angiotensin converting enzyme (ACE) inhibitors. In multivariate analysis the occurrence of non-renal and renal relapses were tested as time-dependent variables. Analyses were performed with SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). A two-sided P value <0.05 was considered to indicate statistical significance.

RESULTS

Between April 1982 and January 1996, 85 patients (55 male, 30 female) were diagnosed with PR3-ANCA positive vasculitis with renal involvement in our hospital. In all patients, a diagnosis of small-vessel vasculitis was confirmed by biopsy. Renal involvement was confirmed in 64 by renal biopsy; in the remaining patients renal failure, erythrocyturia and erythrocyte casts, and proteinuria was present. Age at diagnosis was 56 ± 17 years. Twenty-five patients (29%) were dialysis dependent at diagnosis. Forty-seven patients (55%) had pulmonary involvement, of whom nine patients (19%) needed mechanical ventilation. Organ manifestations are presented in Table 1.

Overall

For the entire group of 85 patients, estimated patient survival at 5 and 10 years was 73 and 62%, respectively (Fig. 1). Causes of death are presented in Table 2. Estimated median survival was significantly shorter in patients >65 years at diagnosis (3.6 years) when compared to those <51 years (17.8 years) and those 51 to 65 years of age (17.0 years; $P < 0.0001$; Fig. 2). The estimated median survival for patients who were dialysis dependent at diagnosis was also significantly shorter than survival in patients who were not on dialysis (9.4 vs. 17.0 years, respectively; $P = 0.013$; Fig. 3). Survival with independent renal function was 65% at 5 years and 51% at 10 years (Fig. 1).

Mortality within one year

Of the 85 patients, 17 patients (20%) died within one year. The main causes of death were active vasculitis, usually within days after diagnosis ($N = 7$), and infectious complications of therapy, between three and six months ($N = 6$; Table 2). Of the seven patients who died of uncontrolled vasculitis, five required dialysis at diagnosis; of the six patients who died of infectious causes, two were dialysis-dependent at diagnosis. Survival within the first year after diagnosis was age-dependent: compared to patients <51 years ($N = 26$) and 51 to 65 years of age ($N = 31$) at diagnosis, patients >65 years ($N = 28$) had a significantly higher risk for death within one year, with a relative risk (RR) of 6.5 (95% CI, 1.6–13.7) and 4.0 (1.4–10.5), respectively. Severe renal involvement was also associated with death within one year (dialysis dependency at diagnosis: RR 2.9 [1.3–10.8]; serum creatinine >500 μmol at diagnosis: RR 2.2 [0.9–6.9]). In multivariate analysis, CRP level at diagnosis, age, and dialysis dependency at diagnosis were associated with mortality ≤12 months (Table 3).

Independence of renal replacement therapy at one year or less

Of the 25 patients who were dialysis-dependent at diagnosis, two did not regain renal function (8%) but survived at one year and nine patients (36%) died within one year (median 1 month, range 4 days to 5 months) without regaining independent renal function. Of 14 patients (56%) who regained independent renal function, two were only temporarily dialysis-independent and needed dialysis again within one year; one died within 12 months. Only 11 of 25 dialysis-dependent patients at diagnosis (48%) were alive at 12 months with a functional renal status. In these 11 patients creatinine clearance at 12 months after diagnosis was 38 ± 14 mL/min. Only one of 60 patients who were dialysis-independent at diagnosis (2%) developed renal failure requiring dialysis therapy within one year after diagnosis. With univariate and multivariate analysis dialysis dependency at diagnosis (RR 29, 95% CI 3.6-229) was the only variable associated with persistent or renewed dialysis dependency within one year after diagnosis (Table 4).

Long-term patient survival

Of 68 patients alive at one year, 27 patients (40%) did not relapse, 10 patients (15%) experienced only non-renal relapses, and 31 patients (46%) had at least one renal relapse, of whom 10 also had one or more non-renal relapses. All relapses were accompanied by the presence of PR3-ANCA at the time of relapse. The median time to the first non-renal relapse was 3.3 years (range 1.6 to 10.5). The median time to the first renal relapse was 4.3 years (range 0.8 to 12.2). Twenty patients died more than one year after diagnosis. In univariate analysis, age >65 years at diagnosis was associated with mortality beyond one year of follow-up compared to age <51 (RR 10.5, 3.6 to 51) and age 51 to 65 (RR 2.9, 1.3 to 11), as was

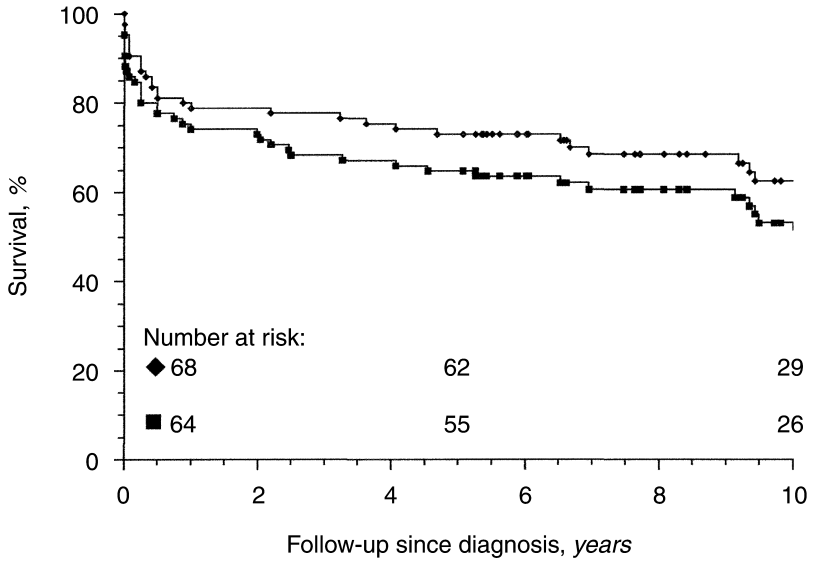

Fig. 1. Patient survival (◆) and survival without need for renal replacement therapy (■) in 85 patients diagnosed with proteinase 3–anti-neutrophil cytoplasmic antibodies (PR3-ANCA) associated vasculitis with renal involvement. Numbers indicate the number of patients at risk at 1, 5 and 10 years after diagnosis.

Table 2. Causes of death

	N (%)	Within 1 year	Follow-up >1 year
Active vasculitis	7 (19)	7	0
Infection[a]	12 (32)	6	6
Malignancy	3 (8)	0	3
Cardiovascular	13 (35)	4	9
Renal insufficiency	2 (5)	0	2
Total	37	17	20

[a] 10 during immunosuppressive treatment

male gender (RR 4.7, 1.6 to 10). In multivariate analysis, development of dialysis dependency was additionally associated with death, but occurrence of renal or non-renal relapses was not (Table 3).

Long-term renal survival

Of 68 patients alive one year after diagnosis, 64 were dialysis independent with a creatinine clearance of 64 ± 31 mL/min (median 60 mL/min, range 18 to 142 mL/min) and proteinuria 0.8 ± 1.0 g/24 h (median 0.3 g/24 h, range 0 to 5 g/24 h) at one year. Mean MAP was 101 ± 10 (median 100, range 83 to 127) at one year and did not change throughout the study period (data not shown). Forty-four patients (65%) were treated with antihypertensives, of which 24 were on ACE-inhibitor and/or angiotensin II antagonist. Twelve of 64 patients (19%) who were dialysis independent at one year progressed to ESRD during the study period; the median time to ESRD in those 12 patients was 4.3 years after diagnosis (range 2.0 to 10.4 years). Five patients who had to start renal replacement therapy (RRT) with the occurrence of a renal relapse (4 patients at the first renal relapse, 1 at the third) did not regain renal function during treatment of the relapse. Five patients developed ESRD after a median follow-up of 3.0 years after their first renal relapse. Only two patients progressed to ESRD without any signs of a renal relapse; these patients had been dialysis dependent at diagnosis. In multivariate analysis the occurrence of a renal relapse and creatinine clearance, but not proteinuria, at 12 months were highly associated with development of dialysis dependency (Table 4). In contrast, non-renal relapses were not associated with reduced renal survival ($P = 0.98$). Dialysis dependency at diagnosis also was not associated with the development of ESRD in long-term follow-up.

Influence of non-renal and renal relapses on renal function

We further analyzed the influence of renal and non-renal relapses on renal function by comparing creatinine clearance and proteinuria before, at the moment of, and following a first relapse. In addition, the slope of the change in creatinine clearance over time was calculated until three months before the relapse and compared with the slope starting three months after a relapse. In 31 patients with a first renal relapse, creatinine clearance at the moment of relapse had decreased by 15 ± 13.0 mL/min compared to 12 months before relapse. At 12 months following the first renal relapse clearance was still 11 ± 11.0 mL/min lower than 12 months before the relapse (Fig. 4A). Proteinuria increased from 0.9 ± 1.2 g/24 h 12 months before, to 2.0 ± 1.6 g/24 h at, and 1.1 ± 1.1 g/24 h 12 months after relapse (Fig. 4B). The slopes of the change in creatinine clearance, excluding the four patients who became dialysis dependent at their first renal relapse, tended to be more negative following as compared to prior to a renal relapse (−1.8 ± 4.5 mL/

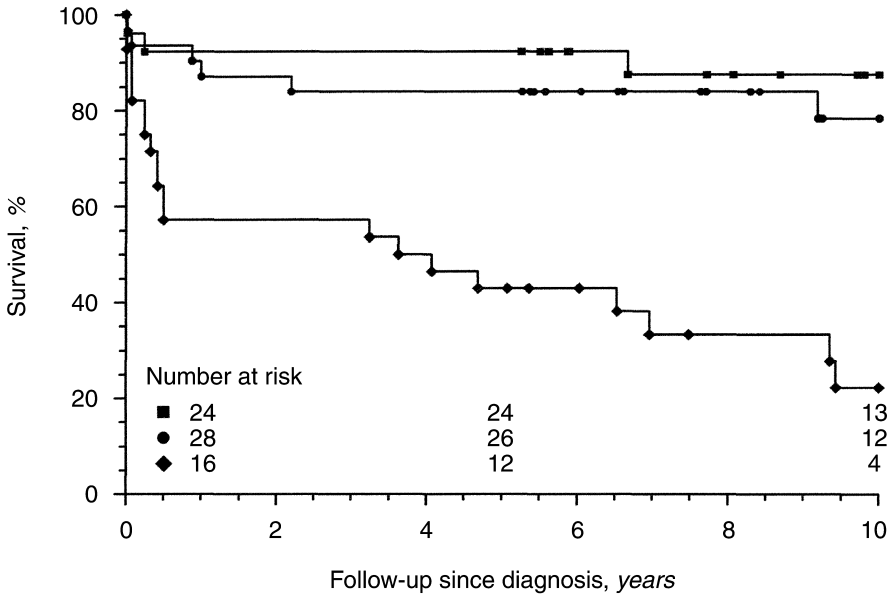

Fig. 2. Patient survival in 85 patients diagnosed with PR3-ANCA associated vasculitis with renal involvement according to age at diagnosis. Symbols are: (■) patients aged <51 at diagnosis; (●) patients aged 51 to 65; (◆) patients aged >65 at diagnosis. Numbers indicate number at risk at 1, 5 and 10 years after diagnosis; $P < 0.0001$. Details are in the text.

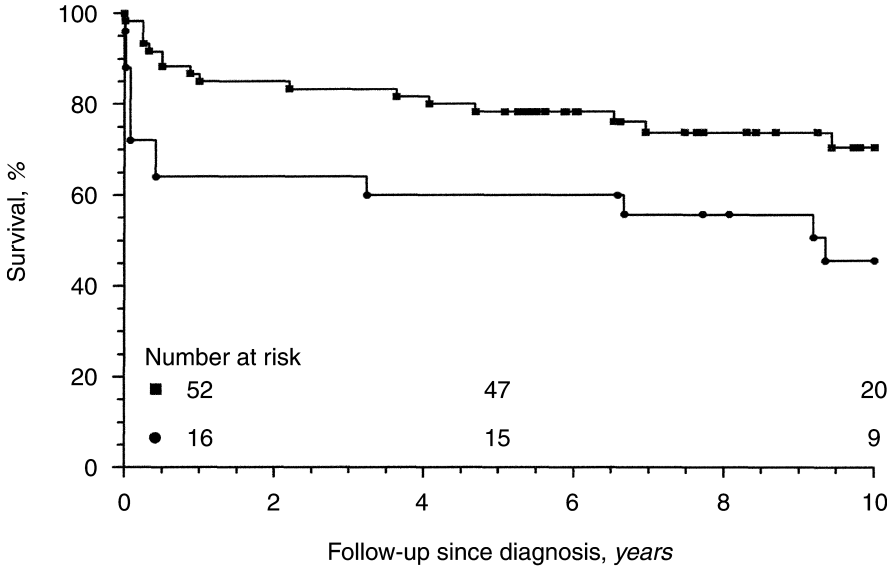

Fig. 3. Patient survival in 85 patients diagnosed with PR3-ANCA associated vasculitis with renal involvement according to dialysis dependency at diagnosis. Symbols are: (■) patients who were not dialysis-dependent at diagnosis; (●) patients who were dialysis-dependent at diagnosis. Numbers indicate number at risk at 1, 5 and 10 years after diagnosis; $P = 0.01$. Details are in the text.

min/year before and -3.1 ± 5.2 mL/min/year after renal relapse; $P = 0.06$). In contrast, a first non-renal relapse was not associated with renal function loss or increased proteinuria at the moment of or following the relapse (Fig. 4). The slopes of the change in creatinine clearance after the first non-renal relapse were not different before and after a non-renal relapse (-1.3 ± 2.0 mL/min/year before and -0.4 ± 1.5 mL/min/year after non-renal relapse).

DISCUSSION

The present study evaluated patient and renal survival in 85 patients with PR3-ANCA associated vasculitis with renal involvement during long-term follow-up. Age >65 years and dialysis dependency at diagnosis were indicative of both poor patient and renal survival. In our long-term follow-up analysis, renal function deteriorated during and after a renal relapse, and the occurrence of a renal relapse was the only predictor of an unfavorable long-term renal prognosis.

The patient survival in our study is comparable to previous studies considering patients with small-vessel vasculitides with renal involvement where it varied from 59 to 95% in various patient groups during various follow-up periods [5, 6, 8, 10, 12, 13, 15, 19]. The mortality rate in our series may be somewhat higher as our department is a tertiary referral center and patients with severe

Table 3. Predictors of patient mortality in multivariate analysis

Predictor	RR	95% CI	*P* value
Patient mortality ≤1 year ($N = 85$)			
Age at diagnosis *1 year increase*	1.10	(1.04–1.16)	0.001
Dialysis dependency *diagnosis*	3.58	(1.01–12.7)	0.05
CRP level *1 mg/L increase*	1.01	(1.00–1.02)	0.045
Patient mortality >1 year ($N = 68$)			
Age at diagnosis *1 year increase*	1.09	(1.03–1.15)	0.002
Male gender	5.75	(1.25–26.5)	0.025
Dialysis dependency *follow-up*	4.15	(1.43–12.0)	0.009

Table 4. Predictors of renal failure in multivariate analysis

Predictor	RR	95% CI	*P* value
Renal failure ≤1 year ($N = 85$)			
Age at diagnosis *1 year increase*			NS
Dialysis dependency	28.6	(3.58–229)	0.002
Renal failure >1 year ($N = 64$)			
Renal relapse	16.8	(3.51–80.8)	<0.001
Creatinine clearance at 12 months *1 mL/min decrease*	1.14	(1.04–1.22)	0.002

disease at diagnosis are referred to our hospital, while patients with less severe disease are often managed at their primary hospital. Mortality shortly after diagnosis is mostly due to uncontrolled vasculitis, while the other important cause is severe infectious complications of the treatment, usually occurring within three to six months after the initiation of treatment. These findings clearly highlight the dilemma the clinician treating these patients must face. Prognostic tools in this respect are therefore important to guide the intensity of treatment. Unfortunately, as reported by others [5, 7, 10, 13, 19], early mortality is strongly associated with older age and more advanced organ dysfunction caused by the vasculitic process. Our results showed that dialysis dependency at diagnosis was associated with early mortality, but in contrast to some other studies [9, 13], lung involvement (with or without the need for mechanical ventilation) was not associated. As can be appreciated from the estimated survival curve, mortality in the first year after diagnosis is different compared to follow-up beyond one year. Therefore, we chose to perform separate analyses for the time periods within and beyond one year after diagnosis. For long-term patient survival, no association of mortality was found with active vasculitis defined as the occurrence of a non-renal or renal relapse; no patients died from active vasculitis beyond one year. Long-term mortality was associated with advanced age (as reported previously [7, 8, 10, 20]), male gender and development of need for dialysis during follow-up.

Fourteen patients (16%) developed ESRD during follow-up (2 of whom within one year), and two patients did not recover from dialysis. Dialysis dependency at diagnosis was highly associated with unfavorable renal

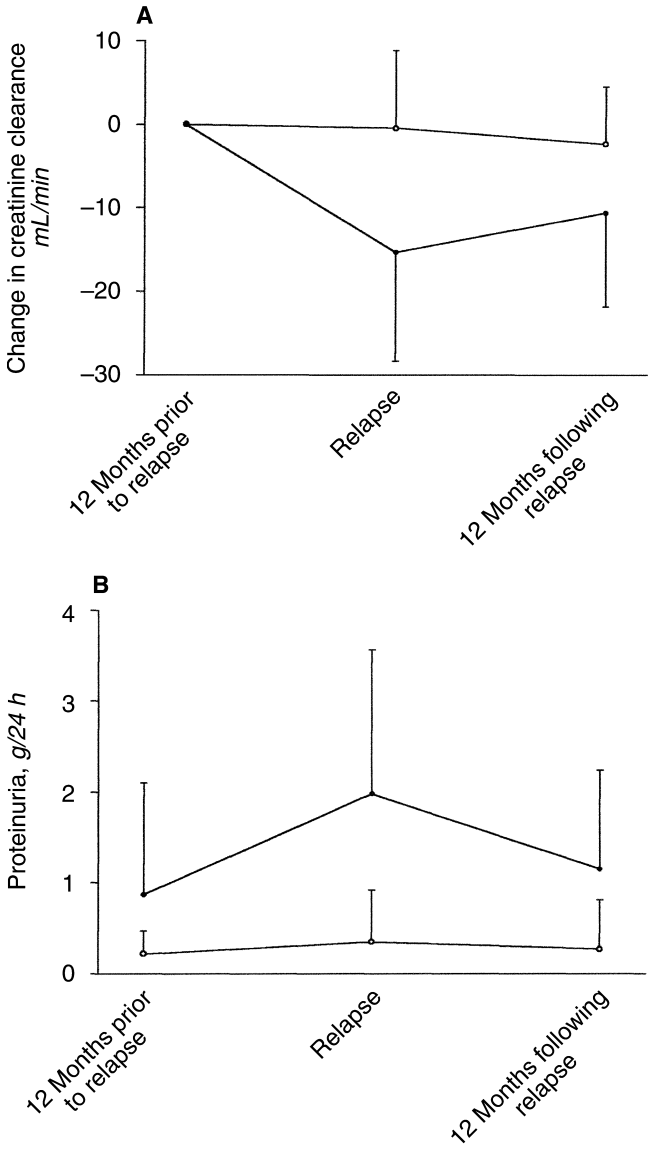

Fig. 4. (A) Creatinine clearances in 44 patients diagnosed with PR3-ANCA associated vasculitis before, during and after the first non-renal or renal relapse. (*B*) Proteinuria in 44 patients diagnosed with PR3-ANCA associated vasculitis before, during and after the first non-renal or renal relapse. Symbols are: (●) patients with a renal relapse; (○) patients with a non-renal relapse. Error bars represent SD.

outcome, as described previously [12, 19, 20]. However, of the 25 patients who were dialysis-dependent at diagnosis and regained independent renal function, 11 regained renal function and they had a mean creatinine clearance of 38 mL/min at one year after diagnosis. We found that dialysis dependency at diagnosis, and not the serum creatinine level, was associated with the development of ESRD, which is in contrast to other studies [8–10, 21]. Renal function at one year after diagnosis was associated with progression to ESRD for patients who experienced a renal relapse during follow-up.

In long-term follow-up, it does seem that relatively

more patients who were dialysis-dependent at diagnosis progress to ESRD. Five of 11 patients who were dialysis-dependent at diagnosis but had functional renal status at one year progressed to ESRD versus five patients of 53 who were dialysis independent at diagnosis and at one year. However, only two patients developed ESRD gradually, without the occurrence of a renal relapse. The other three patients progressed to ESRD after the occurrence of one or more renal relapses. The occurrence of a renal relapse was the strongest independent indicator of a worse renal outcome and carried a high risk for developing ESRD in our patient population. Dialysis dependency at diagnosis per se was not associated with progression to ESRD beyond one year. Long-term renal survival was not associated with blood pressure or proteinuria at 12 months after diagnosis, and renal survival was only related to creatinine clearance at 12 months in multivariate analysis in combination with renal relapse during follow-up. At 12 months after diagnosis renal function was rather well preserved, with a median creatinine clearance of 60 mL/min. In addition, proteinuria was low (median 0.3 g/24 h) and blood pressure well controlled (median MAP 100), characteristics suggesting a low risk for gradual loss of renal function. As the occurrence of renal relapses of PR3-ANCA associated vasculitis was so strongly associated with renal failure, we analyzed the renal function loss associated with renal relapses and the possible influence on progressive renal functional decline. A renal relapse caused a mean long-term loss of creatinine clearance of 11 mL/min and an increase in proteinuria of 0.2 g/24 h. In addition, renal function tended to deteriorate more rapidly after a renal relapse (as measured by the slopes of the change in creatinine clearance). It has been suggested before that the repetitive insults to the renal parenchyma would result in permanent damage [13]. Our observations clearly indicate the amount of damage that a renal relapse in PR3-ANCA associated vasculitis inflicts.

In our study, only two patients progressed to ESRD without signs of a renal relapse. In all other patients, we did not observe a deterioration of renal function in the long-term follow-up unless the patients had a renal relapse, even if patients had been dialysis-dependent at diagnosis. This is clearly in contrast to our findings in MPO-ANCA associated glomerulonephritis, where about one third of the patients can have insidious renal disease ultimately leading to ESRD without active glomerulonephritis. In these patients, proteinuria is an important indicator of deteriorating renal function [15], whereas in our PR3-ANCA vasculitic patients it is not. In the latter, close clinical follow-up for the occurrence of a relapse is needed [22, 23].

In conclusion, for patients with PR3-ANCA associated vasculitis with renal involvement, there are no useful prognostic tools to guide the intensity of treatment. During long-term follow-up, renal relapses are highly associated with an unfavorable renal outcome, and a renal relapse has a significant effect on renal function after this relapse. Since nearly half of the patients with PR3-ANCA experience relapses, physicians should be alerted to the potential consequences of a renal relapse. Efforts to prevent relapses may be the way to preserve long-term renal function in this disease.

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